

Delayed elimination of caffeine by women in the last 2 weeks of pregnancy

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Caffeine elimination was studied in 15 women at 38 to 40 weeks' gestation. The mean hourly caffeine clearance, 37 ml/kg, determined from assays of saliva, was only 39% of the value previously reported for nonpregnant adults (94 ml/kg). Reassessment in four of the women 2 to 12 weeks post partum showed that in each woman the caffeine clearance had increased more than threefold and that the mean caffeine concentration in the saliva after no intake of caffeine for 24 hours was now much lower (0.07 v. 0.84 $\mu\text{g/ml}$).

L'élimination de la caféine a été étudiée chez 15 femmes entre la 38^e et la 40^e semaine de gestation. La clearance horaire moyenne de la caféine, 37 ml/kg, déterminée à partir des dosages de salive, ne comptait que pour 39% des valeurs préalablement signalées pour les femmes non gestantes (94 ml/kg). De nouvelles mesures faites chez quatre femmes de 2 à 12 semaines après l'accouchement ont révélé que chez chacune d'elles la clearance de la caféine avait augmenté de plus de trois fois et que la concentration moyenne de caféine après abstention de caféine pendant 24 heures était maintenant beaucoup plus faible (0.07 comparativement à 0.84 $\mu\text{g/ml}$).

The use of caffeine-containing beverages, consumed at least in part because of caffeine's stimulant effect on the central nervous system and its ability to increase alertness and the capacity for work, is a universal habit that is generally regarded as safe.¹⁻³ Caffeine consumption has been studied extensively, but little attention has been given to the effect on caffeine clearance of factors known to influence drug elimination.

To assess the potential effects of any drug one must consider the rates of both consumption and elimination. Only recently has it been shown that the elimination of caffeine can be influenced by external and internal variables; for example, it is increased in cigarette smokers⁴ and decreased in individuals with liver disease.⁵

A previous study of infants born at term in whom caffeine was transplacentally acquired showed that caffeine elimination was remarkably delayed, compared with that in adults who were nonsmokers, the mean half-lives being 80 and 6 hours respectively.⁶ In addition, the mean caffeine concentration in cord blood (\pm the standard error) was higher than expected (1.5 ± 1.4 $\mu\text{g/ml}$), assuming that the rate of caffeine elimination is the same in both pregnant and nonpregnant women. These findings prompted the present study, in which we

assessed the changes in caffeine elimination in 15 women in the last 2 weeks of pregnancy and post partum.⁷ The results of a study of caffeine elimination throughout pregnancy have been reported elsewhere.⁸

Subjects and method

We studied caffeine elimination in 15 women aged 26 to 36 years at 38 or more weeks' gestation, estimating the duration of gestation from the date of the last menstrual period. All the infants were born at term, when the length of gestation was again assessed and corrected if necessary. All the pregnancies were uncomplicated, except in one woman, who had an episode of threatened premature labour.

All of the women signed an informed consent form before participating in the study. They had either attended a community-based obstetrics practice or were our colleagues. All were in excellent health at the time of the study and had not taken medications known to influence drug metabolism during their pregnancy. However, they had all taken vitamin supplements; as well, three, who had mild edema but no signs of toxemia, had taken hydrochlorothiazide intermittently, two had taken small doses of diazepam intermittently, and one had been successfully treated for premature labour with isoxsuprine hydrochloride before the study.

Four of the 15 women smoked cigarettes regularly and were unable to stop during their pregnancy even after being advised to do so. One woman had stopped smoking in the first trimester and was therefore considered a nonsmoker in this study.

Because four of the women were our colleagues and therefore available for further study, caffeine elimination could be reassessed 2 to 12 weeks post partum.

All of the women received a detailed outline of the procedures to be followed during the study period. In addition, they had been instructed to avoid medications and caffeine-containing foods (they were given examples of the latter) for 24 hours before the study.

On the first morning of the study the women drank 180 ml of a caffeine-containing beverage (coffee or tea) with their breakfast. An aliquot of the beverage was saved and assayed to determine the caffeine level, which averaged 1.2 (extremes 0.35 and 1.9) $\mu\text{g/kg}$. Samples of saliva were collected before the women drank the beverage and at 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 20 hours thereafter; caffeine levels were measured by a radioimmunoassay developed by Cook and colleagues.⁹ The caffeine concentration-time curves were analysed by assumption of a first-order one-compartment model since caffeine is rapidly and completely absorbed and the levels in plasma and saliva decline in a manner consistent with first-order elimination.^{4,10}

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The appropriateness of measuring caffeine levels in saliva has been demonstrated by the fact that those levels are 60% to 90% of the levels in plasma.^{4,10} Although in our study population the levels in saliva generally peaked by 1 hour after ingestion of the beverage, the first level we used for our calculations was that in the sample collected 2 hours after ingestion. The earlier levels were sometimes erratic owing to unexpectedly high saliva concentrations, possibly due to the presence of uningested caffeine-containing beverages in the mouth, although the women had been instructed to rinse their mouths thoroughly after drinking.

Results

The pharmacokinetic measures of caffeine elimination for the 15 women in our study are given in Table I. Caffeine elimination in these women was remarkably delayed compared with that in nonpregnant adults (18 women and 8 men aged 20 to 45 years) studied previously,⁴ the mean hourly clearance values being 37 and 94 ml/kg respectively. Furthermore, the mean half-life of caffeine in nonsmokers was 21.5 hours in the pregnant women and 6.0 hours in the nonpregnant subjects, and in smokers it was 9.6 and 3.5 hours respectively. The relation between caffeine elimination and smoking was maintained; that is, the rate of caffeine elimination was increased in pregnant and nonpregnant individuals who smoked.

In the four women who were available for reassessment 2 to 12 weeks post partum the rate of caffeine elimination had increased more than threefold (Fig. 1 and Table II), mainly because the elimination rate constant increased greatly post partum; there was little change in the volume of distribution. Interestingly, the mean caffeine concentration in the saliva after no intake of caffeine for 24 hours was much higher during pregnancy than post partum (0.84 and 0.07 $\mu\text{g/ml}$ respectively), a finding that is compatible with the delayed elimination of caffeine during pregnancy.

To determine when during pregnancy the changes in caffeine elimination occur, we examined the data for one woman three times during pregnancy and once post partum (Fig. 2), and found that caffeine elimination was most delayed near term and returned to normal by at least 3 weeks post partum.

Discussion

Because drugs are usually avoided during pregnancy few studies have been done of drug elimination during this time. However, certain kinetic changes have been noted; for example, the elimination of pethidine and promazine hydrochloride is decreased during labour,¹¹ and the elimination of phenobarbital and phenytoin may be increased during pregnancy.¹²

We can only speculate as to the reasons for these alterations. In animals oxidative biotransformation of drugs may be impaired by pregnancy and by the administration of reduced progesterone derivatives.¹³ In humans the inhibitory effect of pregnancy on the elimination of caffeine is presumably due to inhibition of the hepatic mixed-function oxidase system; since renal elimination of caffeine is slow, efficient elimination depends on oxidative biotransformation.^{14,15} Interestingly, the use of oral contraceptives decreases the rate of caffeine elimination, which suggests that the hormonal milieu of pregnancy may be responsible for the changes we have reported.¹⁶

Caffeine equilibrates rapidly across the placenta;¹⁷ therefore, the safety of caffeine ingestion during pregnancy has been questioned. In a retrospective study that did not control for smoking habits it was found that spontaneous abortion, stillbirth and prematurity were more common among women who consumed large quantities of caffeine.¹⁸ Linn and coworkers¹⁹ found no such association; however, it is not clear from their study, for which patients were selected if they had completed a pregnancy, whether a change in the rate of spontaneous abortion would have been detected.

Table I—Pharmacokinetic measures of caffeine elimination in 15 women at 38 to 40 weeks' gestation

Subject no.	Half-life (h)	Elimination rate constant (h^{-1})*	Volume of distribution (l/kg)†	Hourly caffeine clearance (ml/kg)‡
Nonsmokers				
1	20.4	0.034	1.80	61
2	12.6	0.055	0.53	29
3	7.7	0.090	0.75	68
4	18.2	0.038	0.55	21
5	27.7	0.025	3.10	78
6	53.3	0.013	0.48	6
7	16.5	0.042	0.88	37
8	13.0	0.053	0.26	14
9	7.6	0.091	0.80	73
10	36.5	0.019	0.10	2
11	23.1	0.030	0.50	15
Mean \pm standard deviation (SD)	21.5	0.045 \pm 0.025	0.89 \pm 0.81	37 \pm 28
Smokers				
12	13.8	0.050	1.60	80
13	12.6	0.055	0.35	19
14	6.1	0.114	0.71	89
15	5.8	0.119	0.66	78
Mean \pm SD	9.6	0.085 \pm 0.032	0.84 \pm 0.46	67§ \pm 27

*Calculated by least-squares log-linear regression analysis of the descending portion of the caffeine concentration-time curve.

†Dose of caffeine divided by extrapolated caffeine level at time zero, after subtraction of level present before caffeine ingestion.

‡Elimination rate constant multiplied by volume of distribution.

§Significant at $P = 0.125$, according to unpaired t -test.

The relevance of the delay in maternal caffeine consumption to these complications is not clear, since the delay may not occur until after the first trimester — that is, after the time of maximum risk of morphologic injury to the fetus.⁸ However, the potential effect of the delay on pregnant women and their offspring in late pregnancy can be hypothesized. If women do not decrease their caffeine intake during late pregnancy, the caffeine level in both mother and fetus could be three times that in nonpregnant women by the end of the pregnancy. Thus, the physical and psychologic effects of this substance could be greater than usual. However, whether adverse effects of caffeine are generally more common in pregnant women remains to be determined.

Delayed elimination of caffeine in a pregnant woman will result in higher than expected levels of transplacentally acquired caffeine in the newborn.⁶ Therefore, the influence of caffeine and of withdrawal of caffeine on

newborn infants merits further investigation. Persons caring for pregnant women and their newborn infants should be aware of the delayed elimination of caffeine in late pregnancy and the possibility of its adverse effects.

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Dr. Parsons was a fellow of the Medical Research Council of Canada at the time of the study.

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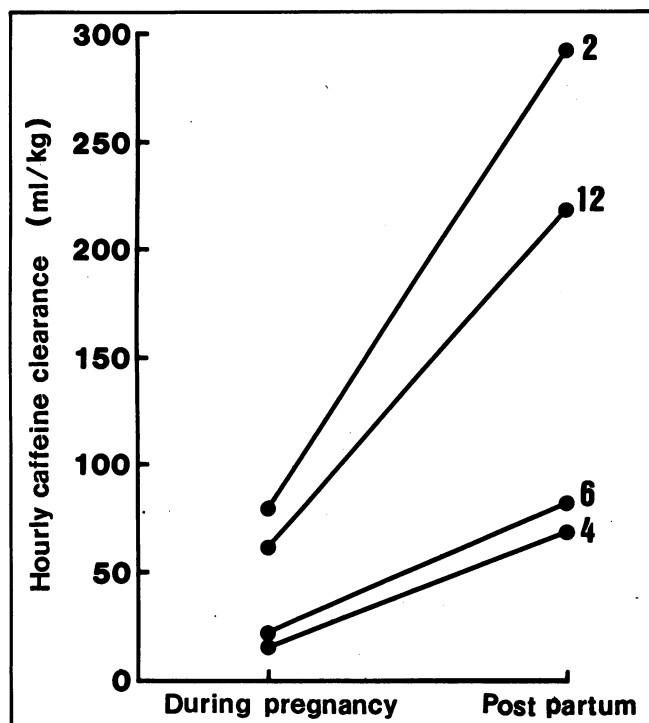


FIG. 1—Plasma clearance of caffeine in four women during pregnancy and post partum. Numbers indicate number of weeks post partum when second assessment was done.

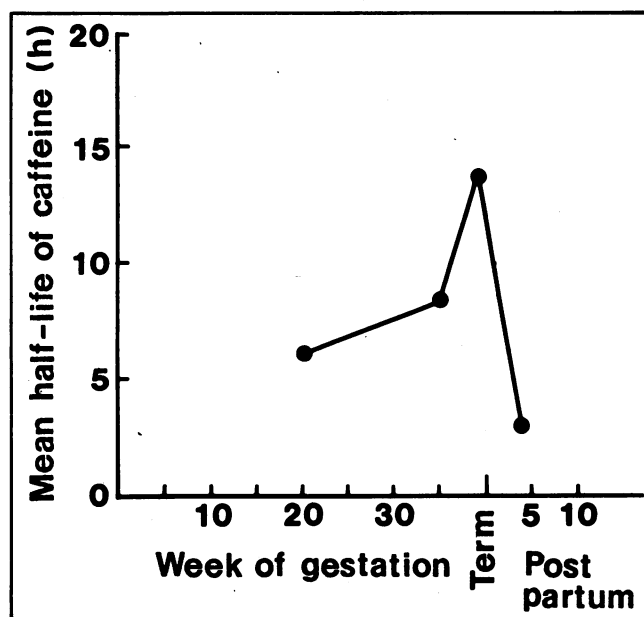


FIG. 2—Mean half-life of caffeine in one woman, assessed three times during pregnancy and once post partum.

Table II—Pharmacokinetic measures of caffeine elimination in four women at 38 to 40 weeks' gestation and 2 to 12 weeks' post partum

Subject no.	During pregnancy				Post partum			
	Caffeine level (μg/ml) at 0 h	Elimination rate constant (h ⁻¹)	Volume of distribution (l/kg)	Hourly caffeine clearance (ml/kg)	Caffeine level (μg/ml) at 0 h	Elimination rate constant (h ⁻¹)	Volume of distribution (l/kg)	Hourly caffeine clearance (mg/kg)
1	1.20	0.034	1.80	61	0.06	0.154	1.42	219
4	0.55	0.038	0.55	21	0.08	0.159	0.52	83
11	0.80	0.030	0.50	15	0.10	0.138	0.50	69
12	0.80	0.050	1.60	80	0.02	0.197	1.48	292
Mean* ± standard error	0.84 ± 0.13	0.038 ± 0.005	1.11 ± 0.34	44 ± 16	0.07 ± 0.017	0.162† ± 0.012	0.98 ± 0.26	166‡ ± 53

*Significant at †P < 0.01 and ‡P = 0.05 according to paired t-test.

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Sex role ideology among physicians

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Physicians have been accused by some feminist writers of having traditional views on sex roles that make them part of society's oppressive power structure and therefore responsible in part for the high incidence of psychologic problems and drug dependency among women. To assess whether physicians' attitudes towards women are indeed polarized in a traditional fashion, a sex role ideology questionnaire was given to all practising physicians belonging to the Manitoba Medical Association. Overall the physicians were found to be more feminist than male college students and a group of women with traditional beliefs. Psychiatrists, who had the highest adjusted group mean score on a sex role ideology scale (high indicating feminist beliefs), were found to be significantly more feminist than family practitioners, surgeons, and obstetricians and gynecologists, although not more so than internists, radiologists, pediatricians and anesthesiologists. These findings do not support the assumption that physicians have traditional views that reflect those of society. However, the significant differences between specialties emphasize the need for educating physicians and medical students in the behaviour of women.

Les médecins ont été accusés par certains écrivains féministes d'avoir des opinions traditionnelles quant aux rôles des sexes, les associant aux forces oppressives de la société et les rendant donc partiellement responsables de la fréquence élevée des problèmes psychologiques et de la dépendance aux médicaments chez les femmes. Afin d'établir si l'attitude des médecins à l'égard des femmes est effectivement polarisée de manière traditionnelle, on a demandé à tous les médecins exerçants, membres de l'Association médi-

cale du Manitoba, de remplir un questionnaire sur l'idéologie du rôle des sexes. Dans l'ensemble les médecins se sont avérés plus féministes que les étudiants collégiaux de sexe masculin et qu'un groupe de femmes ayant des idées traditionnelles. Les psychiatres, qui ont eu la plus forte cote moyenne ajustée de groupe sur l'échelle utilisée (une cote élevée indiquant des idées féministes), se sont montrés significativement plus féministes que les médecins de famille, les chirurgiens et les obstétriciens-gynécologues, mais pas davantage que les internistes, les radiologistes, les pédiatres et les anesthésistes. Ces observations vont à l'encontre de l'hypothèse voulant que les médecins aient des opinions traditionnelles exprimant celles de la société. Toutefois, les différences significatives entre les spécialités soulignent la nécessité de renseigner les médecins et les étudiants en médecine sur le comportement des femmes.

The role of women in society and the effects of society on women have come under increasing scrutiny during the past decade owing to the feminist movement and the increase in the proportion of women professionals. Recently women mental health professionals have taken a closer look at the psychology of women.¹⁻⁶ The results of this research challenge "socially institutionalized sexism"⁵ and, in particular, attitudes towards female patients.⁴

Sex role ideology consists of proscriptive and prescriptive beliefs about behaviour appropriate for men and women. It can be described as a dimension with traditional and feminist poles, a definition that differs from that of gender stereotypes, which are descriptive beliefs about the characteristics and differences between the genders. Traditional sex role ideology maintains that there are basic differences between the sexes, delegating women to the roles of housewife and mother. Furthermore, it maintains that women are weak, vulnerable, in need of protection and deserving of special respect, and that men are the actors, providers and final authorities. Feminist ideology, on the other hand, maintains that

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